IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF SOUTH CAROLINA
CHARLESTON DIVISION

IN RE: LIPITOR (ATORVASTATIN CALCIUM) MARKETING, SALES PRACTICES AND PRODUCTS LIABILITY LITIGATION	**MDL No. 2:14-mn-02502-RMG**
	This document Relates to:
	Wilma A. Daniels v. Pfizer Inc.; Case No.: 2:14-cv-01400

PLAINTIFF'S RESPONSE TO DEFENDANT'S MOTION IN LIMINE TO EXCLUDE REFERENCES TO FOREIGN LIPITOR LABELING AND REGULATORY ACTIONS

Defendant Pfizer is seeking the exclusion of evidence of foreign Lipitor labeling and regulatory actions from the trial of this case. Pfizer argues that such evidence is irrelevant, confusing and prejudicial. Plaintiff disagrees. Evidence of what Pfizer knew and when regarding an increased incidence of new onset diabetes and the aggravation of existing diabetes in patients taking Lipitor is highly relevant. It makes no difference whether Pfizer received notice of those hazards from patients using the drug in Japan or Colorado or South Carolina. Moreover, what Pfizer knew regarding diabetes occurring in Lipitor patients has nothing to do with whether the practices of a given foreign regulatory agency are consistent with or different from those in the United States; any "confusion" about such practices can be easily addressed with an instruction that regulatory agencies have different standards and the acts of one are not binding on another. The critical issue is Pfizer's knowledge of an increased risk of new onset diabetes and the aggravation of existing diabetes in patients taking Lipitor.

Pfizer also claims that the Japanese label change in June 2003 is irrelevant to the claims of Plaintiff Daniels because her diabetes was diagnosed only five months later in November 2003. However, Pfizer could have warned Ms. Daniels and her physicians of the risk of new onset diabetes in that interim period and warned Ms. Daniels's physicians that if she continued on Lipitor after being diagnosed with diabetes the drug might aggravate diabetes. Moreover, the Japanese label change was actually instituted more than a full year after discussion commenced in Japan concerning Lipitor-related hyperglycemic and diabetes adverse events. This chronology is highly relevant, and the jury should be able to consider its importance.

While other pertinent foreign regulatory labeling activities and actions addressed by Pfizer in the present motion, including Pfizer's interactions with the German agency BfArM and the United Kingdom agency MHRA, did occur after Plaintiff Daniels was diagnosed, in all other respects the posture with respect to this evidence is the same. Such evidence is still relevant to Plaintiff's claims in other respects and would not entail confusion or require "mini-trials" on foreign regulatory practices. Pfizer's assertions in this regard are unsupported.

For example, Pfizer's interactions with MHRA reflect Pfizer's knowledge and notice of glucose and diabetes risks associated with ingestion of Lipitor throughout the lifespan of the drug and include in particular evidence of what Pfizer both did and did not do with respect to the study of Lipitor's relation to glucose issues or diabetes over time. MHRA contacted Pfizer in June 2010 and requested, among other things, [redacted][1] Pfizer's response to this and other queries on this issue are certainly relevant to the claims and defenses in this case. Moreover, the data presented in response to the

[1] Exhibit A, Plaintiffs' Exhibit No. 592, at 12 (MHRA response).

queries is precisely the kind of scientific data evaluated by the parties' experts in this case, without regard to the application of any foreign laws or regulations.

Pfizer's communications with BfArM relate specifically to studies Pfizer may cite as proof of Lipitor's efficacy in the prevention of cardiovascular disease (e.g. ASCOT, TNT and IDEAL), and demonstrate Pfizer's direct notice of findings in those studies which contain evidence not only tending to show a lack of efficacy as it relates to women, but even evidence of actual harm to women treated with Lipitor.[2] To the extent Pfizer may put on evidence of Lipitor's efficacy in Daniels or other cases, these interactions and notice to Pfizer of risks and reduced benefit are relevant, if not in Plaintiff's case in chief, then at least in cross-examination of Pfizer witnesses.

I. Facts

Plaintiff intends to offer evidence of foreign regulatory actions in this case to demonstrate what knowledge Pfizer had about the risk of new onset diabetes and the aggravation of existing diabetes, whether in the United States or abroad.[3] The primary example of such evidence is the June 2003 requirement by Japanese regulatory authorities that Pfizer change its Lipitor label to warn physicians regarding onset of diabetes and aggravation of diabetes during Lipitor use.[4] This action occurred after [redacted][5] Further, Pfizer declined to inform FDA of the June 2003 label change, despite informing FDA the year before of a more modest labeling

[2] Exhibit B, Plaintiffs' MDL Exhibit Nos. 2132 and 4810 (BfArM Preliminary Variation Report).
[3] As noted, Plaintiff does not intend to offer evidence of foreign regulatory laws or standards and believe that "confusion" in this regard, if any, can be addressed by an instruction that regulatory agencies have different standards and that acts of one are not binding on another.
[4] Exhibit C, Lipitor MDL Plaintiffs' Exhibit No. 3150 (English translation of Japanese Lipitor label).
[5] Exhibit D, Lipitor MDL Plaintiffs' Exhibit No. 3226 (reasons for change from Yamanouchi).

event in Japan, and despite regulatory guidance instructing that Pfizer should have informed FDA of the change.[6] Finally, Pfizer declined to inform physicians in the U.S. about the events, even in the face of specific inquiries from U.S. physicians about a relationship between Lipitor and glucose abnormalities in the immediate aftermath of the change.[7]

Pfizer first received notice of the Japanese [redacted][8] A memorandum reflecting a meeting with [redacted]

By November 2002, Pfizer was advised that [redacted][10] And by the next month, December 2002, Pfizer was aware that [redacted]. As Pfizer notes, it had Rajesh Aggarwal review the adverse event reports received from Yamanouchi. However, Aggarwal is not a medical doctor, does not regard himself as an expert

[6] Exhibit E, Expert Report of Gilbert Alexander Fleming report with Guidance, at 30-31.
[7] Exhibit F, Deposition of Barbara LePetri, M.D., 220:13 – 222:23; 225:4-8; 225:12 – 228:14; 229:17; 229:20 – 230:9; 230:12-13; 230:15-23.
[8] Exhibit G, Lipitor MDL Plaintiffs' Exhibit Nos. 3191, 3510 and 3511.
[9] *Id.* in Exhibit G, Lipitor MDL Plaintiffs' Exhibit No. 3511.
[10] Exhibit H, Lipitor MDL Plaintiffs' Exhibit No. 4094.

in the diagnosis or treatment of diabetes and has never done any research on diabetes.[11] Aggarwal and Pfizer dismissed the cases, asserting that the reports [redacted]" and concluded no change to the labeling was warranted.[12] However, Yamanouchi had actual medical doctors review the cases, and it reached the opposite conclusion.[13] In May 2003, the MHLW recommended that the Lipitor label be updated to advise diabetic patients taking Lipitor that their condition could be "aggravated," and to advise all patients taking Lipitor that diabetes and hyperglycemia were "clinically significant adverse reactions" that could occur while taking Lipitor and that they should be "observed carefully" for symptoms of such conditions. Not surprisingly, as it notes, Pfizer disagreed with these changes, which were viewed within the company as having [redacted] to the Lipitor label.[14] The label change went into effect in June 2003, and it was brought to the attention of Dr. Joseph Feczko, Pfizer's Chief Medical Officer, and other Pfizer executives, on July 16, 2003 in a Medical and Regulatory Monthly Report for June 2003.[15] The Report advised Dr. Feczko and the other executives that the [redacted][16]

Several months after the change went into effect in June 2003, Pfizer failed to report it to either FDA or EMA (the European Medicines Agency, the European Union equivalent of the FDA) as part of its periodic update reporting to those agencies, notwithstanding that it had reported on far less serious changes to the Japanese label – regarding sleepiness, dysgeusia and

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[11] Exhibit F, Deposition of Barbara LePetri, M.D., 100:7 – 101:23 and Exhibit I, 30(b)(6) Deposition of Rajesh Aggarwal, Ph.D., 15:5-11.
[12] Exhibit J, Lipitor MDL Plaintiffs' Exhibit Nos. 273, 277 and 278.
[13] Exhibit K, Lipitor MDL Plaintiffs' Exhibit No. 3226 and Exhibit L, Deposition of Rajesh Aggarwal, Ph.D., 175:22 – 181:6.
[14] Exhibit M, Lipitor MDL Plaintiffs' Exhibit Nos. 522 and 218.
[15] Exhibit N, Lipitor MDL Plaintiffs' Exhibit Nos. 4200 and 307.
[16] *Id.*

urinary frequency – in its report to EMA in 2002.[17] Aggarwal testified individually and on behalf of the company as a 30(b)(6) representative that Pfizer's rationale for declining to tell FDA about the change was simply that it disagreed the change was valid and appropriate and did not believe it would be of value to U.S. prescribing physicians and patients.[18]

Pfizer disagrees with the opinion of Plaintiffs' regulatory expert Dr. Fleming that a 2001 FDA Guidance instructed U.S. entities to report on "important foreign regulatory actions (e.g., new warnings, limitations in the indication and use of the product)."[19] Pfizer does not address this Guidance in its motion, but its position, as expressed by its regulatory expert Dr. Rarick, is that the Guidance does not apply because the 2003 label change was, for a variety of reasons, not "important."[20] Clearly, this disagreement among experts is a matter for the jury to determine. Pfizer also engages in a lengthy discussion of Dr. Fleming's views concerning the differences between the U.S. and Japanese regulatory systems and notes his comments concerning specific language selected by the MHLW for the Japanese label.[21] However, this discussion is entirely beside the point. Dr. Fleming's opinion is that regardless of these differences or any disagreements that he (or Pfizer) might have with the label language, Pfizer should have advised the FDA about the label change. Finally, Pfizer makes the self-evident argument that Dr. Fleming cannot say with certainty what FDA would have done had Pfizer advised it of the label change. Of course he cannot say with certainty what FDA would have done; but he can and does

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[17] Exhibit I, 30(b)(6) Deposition of Rajesh Aggarwal, Ph.D., 101:8 – 106:17.
[18] Exhibit I, 30(b)(6) Deposition of Rajesh Aggarwal, Ph.D., 92:10 – 94:6.
[19] Exhibit E, Expert Report of Gilbert Alexander Fleming, at 30-31.
[20] Exhibit O, Expert Report of Lisa Rarick, M.D., at 67-68.
[21] Pfizer twice quotes Dr. Fleming's use at his deposition of the term "silly" to describe a particular recommendation in the Japanese label, namely that "discontinuing treatment" of Lipitor might be an "appropriate measure." Pfizer motion at 2 and 14. Pfizer neglects to note that Dr. Fleming retracted that word later in his deposition and commented that, "I think there could be occasions when it would be appropriate to [discontinue treatment]." Exhibit P, Deposition of Gilbert Alexander Fleming, 323:14-23.

say with certainty that Pfizer should have so advised FDA such that FDA could have considered this highly pertinent information in 2003.[22]

Pfizer also chose not to share any information regarding the adverse events or labeling issues in Japan with U.S. physicians or patients. Beginning at least as early as January 2003 Pfizer began receiving inquiries from U.S. physicians about Lipitor and glucose issues.[23] The inquiries in early 2003 related to an article in the LA Times discussing Lipitor and elevations of blood sugar.[24] In response to inquiries from physicians, Pfizer used Medical Information letters developed by the medical information group within the company.[25] Further inquiries concerning glucose issues arose after the presentation of the PROVE-IT-TIMI sub-study results in late 2004. In responding to such inquiries in mid-2005, over two years after the label change in Japan, Pfizer failed to disclose clearly relevant information to U.S. physicians, even in the face of direct inquiries on the subject.[26] The Medical Information letter, which was revised after the PROVE-IT-TIMI sub-study and the Japanese label change, gives only scant, carefully selected information on Pfizer clinical trial data and mentions nothing of the Japanese adverse events or label change. Pfizer's actions here with respect to U.S. physicians can certainly be assessed by the jury without regard to any foreign regulations or laws, but with the application of the relevant standards applicable to Pfizer's conduct here in the U.S.

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[22] Exhibit E, Expert Report of Gilbert Alexander Fleming, at 30-31.
[23] Exhibit F, Deposition of Barbara LePetri, M.D., 158:8-13.
[24] Exhibit Q, Lipitor MDL Plaintiffs' Exhibit Nos. 267 and 5089; Exhibit F, Deposition of Barbara LePetri, M.D., 165:4-24; 166:20 – 168:11; 170:4-10.
[25] *Id.* and Exhibit U, Lipitor MDL Plaintiffs' Exhibit Nos. 3523 and 3524; Exhibit F, Deposition of Barbara LePetri, M.D., 158:19 – 162:2 and 211:9 – 214:8.
[26] Exhibit R, Lipitor MDL Plaintiffs' Exhibit Nos. 3553 and 3554; Exhibit F, Deposition of Barbara LePetri, M.D., 220:13 – 222:23; 225:4-8; 225:12 – 228:14; 229:17; 229:20 – 230:9; 230:12-13; 230:15-23.

This evidence is relevant and admissible on the issues of Pfizer's notice of the risk of diabetes as well as being relevant to demonstrate Pfizer's state of mind and motivation in failing to inform FDA of the change or to warn physicians similarly in the U.S. Moreover, as the chronology of events demonstrates, Pfizer was advised of the inquiries about elevated blood glucose in Lipitor patients - concerns that ultimately led to the Japanese label change - well over a year before Plaintiff Daniels was diagnosed with diabetes.

II. Argument

Under the Federal Rules of Evidence, evidence is relevant if two criteria are satisfied: "it has a tendency to make a fact more or less probable than it would be without the evidence; and the fact is of consequence in determining the action."[27] Plaintiff's burden of proof in this case requires that she show, among other things, that Lipitor posed a risk of injury to one who used the product and that Pfizer had notice of the risks presented by Lipitor, i.e., that those risks were foreseeable. The evidence described above is relevant and probative on these issues and others.

Pfizer intentionally misstates the purpose of the offer of certain foreign labeling documents and Pfizer's internal communications. This evidence does not bear on whether foreign actions are binding on Pfizer in the U.S. or on the differences between U.S. and foreign regulations. Rather, the evidence bears on Pfizer's knowledge, the timing of its knowledge and the actions taken in the face of that knowledge. The question of liability in this case turns on whether Lipitor posed a risk of harm, whether Pfizer knew or should have known of those risks, and whether Pfizer adequately warned of the known or knowable risks. Relevant state or federal law and standards will determine whether Pfizer's Lipitor label was adequate.

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[27] Fed. R. Evid. 401.

Presenting evidence of a foreign product label or regulatory action does not require or necessitate an examination or application of the pertinent foreign law. The evidence is being presented to show that a particular risk existed and that Pfizer had notice of it. That Pfizer's Lipitor label carried a warning of a particular risk in a foreign jurisdiction certainly makes it more probable that such a risk indeed existed, and that Pfizer itself had notice of that risk or that the risk was scientifically knowable.[28] The evidence further demonstrates that Pfizer had notice of the effect of this warning on physician prescribing practices and that it would likely reduce sales.

The cases cited by Pfizer in support of its motion to exclude this evidence are largely distinguishable. Some stand for the proposition that the examination or application of a foreign jurisdiction's laws, regulations or standards is inappropriate in an action in this country.[29] As noted above, Plaintiff is not seeking the application of any foreign law, nor seeking to have Pfizer's actions measured by any foreign standards. Clearly, this Court has the discretion to exclude otherwise relevant evidence if its probative value is outweighed by other considerations. However, evidence of foreign regulatory action, events or even standards is not per se inadmissible.[30] In fact, courts have often found such evidence admissible.[31]

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[28] Under federal regulations governing Pfizer's Lipitor label or package insert, a manufacturer is obligated to "include a warning about a clinically significant hazard as soon as there is reasonable evidence of a causal association with a drug; a causal relationship need not have been definitely established." *See* 21 C.F.R. § 201.57(c)(6). The Japanese regulatory action and label also provided further notice to Pfizer of "reasonable evidence of an association of a serious hazard" with Lipitor.

[29] *Hurt v. Coyne Cylinder Co.*, 956 F.2d 1319 (6th Cir. 1992); *Harrison v. Wyatt Laboratories, et al.*, 510 F. Supp. 1 (E.D. Pa. 1980); *Garmon v. Cincinnati, Inc.*, 1993 WL 190923 (Tenn. Ct. App. June 4, 1993).

[30] *See In re Rezulin Prods. Liab. Lit.*, 309 F. Supp. 2d 531, 552 (S.D.N.Y. 2004) (refusing to find evidence of foreign regulatory action irrelevant as a matter of law); *Sherry v. Massey-Ferguson, Inc.*, 1997 WL 480893 (W.D. Mich. 1997) (finding neither *Hurt* nor *Deviner, supra,* held foreign

Recently, both MDL and non-MDL courts have allowed the admission of foreign regulatory evidence. For example, in 2012 in the Chantix multidistrict litigation, Judge Inge Johnson denied Pfizer's motion to exclude evidence of foreign labeling, citing, among other support, a 2011 order from the Yaz multidistrict litigation.[32] The Yaz court found that evidence relating to foreign regulatory actions and the defendant's reaction to them were relevant and admissible as "well within the notice and knowledge" of the defendant in that case.[33] The Yaz Court further noted:

> While the regulatory actions of European Medical regulators are not binding on the FDA—a fact that should be made clear to the finders of fact in this case to avoid confusion—the full body of knowledge including the foreign regulatory process that came to bear on the drugs at issue and which were well within the notice and knowledge of Bayer is admissible as part of the fabric of how these drugs came to the United States market and whether all the information which should have been utilized in doing so was utilized. Such evidence is clearly probative and that value outweighs the prejudice to Bayer.

In re Yasmin & Yaz (Drospirenone) Mktg., Sales Practices & PMF Products Liab. Litig., No. 3:09-CV-10012-DRH, 2011 WL 6740391, at *2 (S.D. Ill. Dec. 22, 2011). The Yaz Court's suggestion of a jury instruction to eliminate any possible prejudice or confusion is particularly appropriate here, as those are Pfizer's principal objections to the introduction of foreign regulatory evidence.

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legal standards inadmissible as a matter of law); *Slisze v. Stanley-Bostich*, 979 P.2d 317, 322 (Utah 1999) (rejecting a bright-line rule against admitting foreign safety standards).

[31] *See Sherry, supra,* *2 (finding evidence of a foreign tractor design relevant to feasibility of design alternative and defendant's knowledge of such alternatives); *Orjias v. Stevenson*, 31 F.3d 995, 1000 (10th Cir. 1994) (affirming admission under Rule 404(b) of evidence of foreign plaintiffs' letters to defendant regarding environmental violations as probative on the issue of defendant's notice or knowledge of issues therein); *Larue v. National Union Electric Corp.*, 571 F.2d 51, 57 (1st Cir. 1978) (affirming admission of evidence regarding safety shield required by foreign regulations).

[32] Exhibit S, Chantix order.

[33] Exhibit T, Yaz order.

Apart from the Chantix and Yaz MDLs, Judge Weinstein, in ruling on summary judgment motions in the Zyprexa multidistrict litigation, discussed evidence of foreign labeling similar to that in this case, thus implicitly recognizing it as relevant and admissible evidence.[34] Judge Weinstein specifically noted variances in the timing of warnings – specifically that other countries had required warnings prior to FDA – in international labels, as well as differences in the specific language of the various labels. Additionally, the facts in the Zyprexa case were strikingly similar to this case in that there was a warning issued in Japan shortly after the introduction of the drug into that market, again based on the accumulation of serious adverse event cases. As in this case, the warning in the U.S. came later, but the defendant's knowledge of the facts surrounding the labeling event in Japan and other countries was relevant to the court's decision-making process.

Similarly, the court in *Mahaney ex rel. estate of Kyle v. Novartis Pharm. Corp.* refused to prohibit the introduction of foreign package inserts, stating "[b]ecause the company transcends international boundaries, the labeling in other countries could bear on what information the company's executives were privy to and when they recognized the alleged connection between Zometa [the drug at issue] and ONJ [the injury]. The Court will permit this evidence, as it may bear on NPC's knowledge and the notice it had of Zometa's side effects."[35] The same rationale applies here: Pfizer is a huge corporation operating multi-nationally and acquiring knowledge about its products from all the countries in which it operates. Plaintiff seeks to show evidence of the knowledge that Pfizer acquired, from whatever location it was acquired, as that directly bears on the all-important issue of notice.

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[34] *In re Zyprexa Prods. Liab. Lit.*, 489 F. Supp. 2d 230, 250 (E.D.N.Y. 2007).
[35] 835 F. Supp. 2d 299, 318 (W.D. Ky. 2011).

Pfizer's motion is largely dependent upon older MDL case law that has been distinguished or set aside by more recent MDL rulings. For example, the Court in *In re Seroquel Prod. Liab. Litig.*, did exclude foreign regulatory evidence because it viewed these materials as prejudicial to the defendant and possibly confusing for the jury.[36] Similarly, the Court in *In re Baycol Prod.Liab. Litig.* held that the foreign regulatory evidence would be confusing to the jury.[37] However, the more recent trend of MDL courts, as discussed above, has been to allow such evidence. Indeed, the court in *In re Levaquin Products Liability Litigation* took direct issue with the reasoning of the *Seroquel* and *Baycol* courts, stating "the Court finds it unlikely that a jury would be confused and simply defer to the foreign regulatory action, since the substance of the regulatory action is itself in dispute. As a result of these factors, the Court denies the motion only so far as to allow the evidence for the purposes of showing notice and motive."[38] This Court should continue this trend and allow the introduction of foreign regulatory evidence. Any potential for confusion or prejudice can easily be dispelled by a jury instruction as suggested by the Yaz MDL court.

Pfizer's reliance upon *Meridia Prods. Liab. Litig. v. Abbott Labs.*, 447 F.3d 861 (6th Cir. 2006) is similarly misplaced. In *Meridia*, the plaintiffs argued that the difference in the foreign labeling compared to the American labeling created a triable issue of fact. The Sixth Circuit disagreed. This line of argumentation is wholly irrelevant here. Plaintiff is not arguing that the Japanese label change creates a triable issue of fact. Rather, Plaintiff believes that the Japanese label change and the reports and communications leading up to it demonstrate Pfizer's notice that

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[36] 601 F.Supp. 2d 1313, 1315 (M.D. Fla. 2009).
[37] 532 F. Supp. 2d 1029, 1054 (D. Minn. 2007).
[38] *In re Levaquin Products Liab. Litig.*, No. 08-1943 JRT, 2010 WL 4676973, at *5 (D. Minn. Nov. 9, 2010)

Lipitor causes diabetes. Again, properly crafted jury instructions can easily place foreign labelling evidence in the proper context for the jury.

In sum, the purposes for which Plaintiff seeks the admission of this evidence do not present the risks invoked by Pfizer. The jury will not have to examine foreign laws, regulations or standards, nor will it have to apply them to Pfizer's conduct. Rather, the jury will be asked to apply relevant state or federal law and standards to the facts in this case, including the fact that Japanese regulatory authorities required Pfizer to issue the warning in Exhibit C. This process does not require an examination of foreign law or standards, much less of political or social customs as Pfizer suggests. Whether the foreign regulators' actions were appropriate or valid is neither at issue nor relevant. What is relevant is that the actions occurred and that Pfizer had knowledge of and reacted, or should have reacted, to them.

For the reasons stated above, the Court should deny Pfizer's Motion in Limine.

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Respectfully Submitted,

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